This Month in *The Journal*

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Structural Variation: The Clone Wars

Forsberg et al., page 217

DNA is often viewed as an individual's blueprint, but changes can and do occur over time, leading to populations of cells that possess distinct genotypes. For example, environmental insults can reduce replication fidelity, leading to increased cancer susceptibility. Much less is known, however, about somatic mosaicism comprising large-scale structural variation. How widespread a phenomenon this is and whether the aging process alone causes such variation remain poorly defined. In this issue, Forsberg et al. address these questions through the longitudinal analysis of both twins and singletons. Notably, they find evidence of age-related accumulation of structural variation on both the kilobase and megabase scales. The rate of change is variable across individuals, and interestingly, some of the changes "disappear" with time, suggesting that genomic clonal battles are a common occurrence. Moreover, the authors note recurrent region- and gene-specific mutations, including some that are characteristic of myelodysplastic syndrome. Why and how such changes develop over time and whether disease or the loss of "rogue" clones is the typical outcome remain unknown. Indeed, although intriguing, these findings serve as a launching pad for future research. As technology advances, it will be possible to detect ever-smaller copy-number gains and losses with high fidelity, thus allowing us to gain a better understanding of how aging affects our DNA.

Methylation on the Brain

Numata et al., page 260

Even for neurobiologists, the inner workings of the brain remain an enigma. What is it that shapes our personalities, and how do genetic and/or epigenetic changes translate into dramatic disease states? In one approach to addressing this question, Numata et al. examine global methylation patterns in the prefrontal cortex. The developmental program of this brain region, which is critical for the development of personality and helps to orchestrate complex cognitive processes, is incompletely understood. The authors show that methylation patterns change rapidly during early development, especially during the transition from fetal to postnatal life. Given the suspected role that the in utero period has on the development of several neurodevelopmental disorders, including schizophrenia and autism spectrum disorders, it is possible that discrete alterations in methylation patterns play a role in their etiology. Indeed, the authors identify age-related methylation changes in the promoter regions of several genes implicated in this family of disorders. The authors also describe several sex-biased changes in autosomal methylation patterns, thus paving the way for future research related to both the normal biology and the pathological differences in the male and female brain. Epigenetics is often referred to as the bottom of a so-called genomic iceberg; with this work, perhaps the tip just got a little bigger.

Mirror, Mirror on the Wall

Depienne et al., page 301

While playing, young children reaching for an object with their right hand often also move their left hand in an apparent mirror image. These involuntary movements are normal during the period of neuronal maturation, but such movements can persist pathologically in adults. Individuals who display congenital mirror movements are unable to perform simple motor tasks and therefore find everyday life to be extremely challenging. In this issue, Depienne et al. use both linkage analysis and exome sequencing to uncover the cause of this motor defect. Unexpectedly, they identify mutations in *RAD51*, a gene whose protein product is known to play a crucial role in the repair of DNA double-strand breaks. This finding not only sheds new light on the genetic underpinnings of congenital mirror movements, but it also suggests that our understanding of the molecular function of RAD51 is far from complete. Future experiments on mice and other model systems should help to unravel the role that RAD51, either in conjunction with its known binding partners or as part of still-undefined complexes, plays in brain development.

The First Steps out of Africa

Fernandes et al., page 347

The history of early humans both fascinates and frustrates: The desire to learn where we came from is often stymied by a lack of meaningful evidence. Although it is common

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knowledge that humans originated in Africa, the nature of the path taken on the way to populating Europe and Asia has remained controversial. One model posits that early humans crossed the Red Sea into southern Arabia. Genetic data to support this model have, however, been lacking. In this issue, Fernandes et al. address this hypothesis through the careful analysis of three rare, geographically dispersed west-Eurasian mitochondrial haplogroups (N1, N2, and X). By comparing over 300 mitochondrial genomes belonging to these haplogroups, the authors show that members of these non-African lineages share an ancient Arabian ancestry, coalescing 60,000 years ago, a time frame consistent with out-of-Africa migration into western Eurasia. Together with corroborating archaeological evidence, these findings provide strong support for the idea that Arabia was a major staging area for the spread of modern humans.

Splice it Up!

Lines et al., page 369

mRNA splicing is responsible for the enormous diversity in the human proteome, but as with any crucial cellular process, there are many opportunities for things to go awry. However, although there are many examples of diseases caused by splicing-donor or receptor-site mutations, there are relatively few known instances of defects in the splicing machinery itself. In this issue, Lines et al. demonstrate that mutations in *EFTUD*, which encodes a spliceosomal GTPase thought to regulate both splicing and spliceosomal disassembly, cause mandibulofacial dysostosis with microcephaly. A variety of de novo mutations, including missense and nonsense mutations, frameshifts, and deletions, were observed, suggesting haploinsufficiency as the cause. Although mutations in *EFTUD* have not been previously identified, research from budding yeast provides great insight into its function. Interestingly, several of the newly identified human mutations correspond to known temperature-sensitive mutations. Armed with this knowledge, the authors propose a mechanism by which these mutations disrupt protein function. Future research will be focused on understanding not only how *EFTUD* mutations cause this complex disease, but also how dysregulation of other spliceosomal components can elicit completely different spectrums of phenotypes. Clearly, there is still much to learn about the genetics of splicing.